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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,164	07/24/2001	Jose Repolles Moliner	14797	4564

7590 09 09 2003

SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, NY 11530

[REDACTED] EXAMINER

LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	11

DATE MAILED: 09 09 2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/912,164	MOLINER ET AL.
	Examiner	Art Unit
	David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 27 June 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 19-37 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 19 and 28-37 is/are rejected.

7) Claim(s) 20-27 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .	6) <input type="checkbox"/> Other: _____ .

Pursuant to the directives of paper No. 10 (filed 6/27/03), claims 1-9, 12-18 have been cancelled, and claims 19-37 added. Claims 19-37 are pending. Applicants' arguments filed 6/27/03 have been considered and found persuasive. The previously imposed rejections are withdrawn.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To begin with, it is stipulated that the following claims are enabled:

A method of inhibiting vasoconstriction comprising administering the S-nitrosothiol derivative according to claim 19 to a subject in need thereof for a time and under conditions effective to inhibit vasoconstriction.

A method of inhibiting platelet aggregation comprising administering the S-nitrosothiol derivative according to claim 19 to a subject in need thereof for a time and under conditions effective to inhibit platelet aggregation.

A method of inhibiting platelet aggregation comprising contacting platelets with the the S-nitrosothiol derivative according to claim 19 for a time and under conditions

effective to inhibit aggregation of said platelets.

A method of stimulating platelets to produce cGMP comprising administering the S-nitrosothiol derivative according to claim 19 to a subject in need thereof for a time and under conditions effective to stimulate said platelets to produce cGMP.

A method of stimulating platelets to produce cGMP comprising contacting platelets with the S-nitrosothiol derivative according to claim 19 for a time and under conditions effective to stimulate said platelets to produce cGMP.

Applicants have shown that (a) the claimed compounds can inhibit (pp. 29-30) norepinephrine-induced vasoconstriction *in vitro*, (b) the claimed compounds can inhibit (pp. 30, 31, 33, 34) platelet aggregation *in vitro*, and (c) the claimed compounds can stimulate (pp. 31-32) platelets to produce cGMP. Based on this, applicants are asserting that the claimed compounds can be used to treat any and all "circulatory dysfunctions".

Claim 28 is drawn to a method of treating "circulatory dysfunctions", and claims 29-37 are drawn to a "pharmaceutical" composition. The term "pharmaceutical" implies an assertion of therapeutic efficacy, which is not in evidence.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or

unpredictability of the art. and breadth of the claims. As it happens, use of ACE inhibitors (angiotensin converting enzyme inhibitors) to treat cardiovascular diseases produces "unpredictable" results. Consider the following:

- Wilson (Cardiovascular Research 42 (3) 761-72, 1999) has examined the effect of ACE inhibition on vascular injury/ restenosis, and reports that ACE inhibition has proven ineffective in clinical trials.
- Koerner (*Journal of Cardiovascular Pharmacology* 17 (2) 185-91, 1991) has studied treatment of postischemic myocardial dysfunction in anesthetized rabbits. Koerner reports that enalaprilat was not effective when given alone.
- Linz (*Journal of Cardiovascular Pharmacology* 15 Suppl 6 S99-109, 1990) reports that while some efficacy was observed when the ACE inhibitor ramiprilat was administered in conjunction with BK, ramiprilat was ineffective when administered alone.
- Billaud-Mesguich E (Revue de Medecine Interne 7 (5) 543-7, 1986) discloses (abstract) that Enalaprilate is an ACE inhibitor that is not directly absorbable. It is therefore administered as an inactive precursor, an enalaprilate ester which is hydrolysed in vivo. This reference supports the assertion that where ACE inhibition is concerned, one cannot "predict" bioavailability based on *in vitro* data alone.
- Huckle W R (*Circulation* 93 (5) 1009-19, 1996) discloses that ACE inhibitors have not been effective in nonhuman coronary models or in human restenosis trials.
- Edling, Oliver (*Journal of Pharmacology and Experimental Therapeutics* 275 (2), 854-863, 1995) discloses that (a) the antihypertensive potency of a given ACE inhibitor cannot be predicted from its *in vitro* characteristics and (b) the degree of blood pressure reduction **does not correlate** with tissue ACE inhibition.
- Grover G. J. (*J Pharmacol Exp Ther* 257 (3), 919-929, 1991) discloses that neither zofenopril nor captopril had any effect on coronary flow before or after ischemia, and that the cardioprotective effects of zofenopril and captopril are independent of cardiac ACE inhibition or, at least, that ACE inhibition alone is not sufficient.

The question of what effects one can expect following inhibition of angiotensin is relevant to the claimed invention. Applicants have asserted that the claimed compounds can mitigate vasoconstriction. Thus, the question is, can one "predict" efficacy in the treatment of circulatory disorders following mitigation of vasoconstriction? The literature supports the conclusion that "unpredictable" results are obtained when the skilled cardiologist attempts to treat circulatory disorders in patients by inhibiting vasoconstriction.

One may also look to the literature on antithrombic agents. Consider the following:

- Steinmetzer, T. et al, (*Expert Opinion on Investigational Drugs* **10** 845-64, 2001) discloses (e.g., abstract) that there are thrombin-mediated illnesses for which heparin, warfarin and aspirin are ineffective, even though these compounds exhibit antithrombic activity. The reference also discloses (page 857, col 2, last sentence) that there exists at least one compound which is an effective thrombin inhibitor *in vitro*, but is not effective *in vivo*.
- Rutsch, W. et al (*European Heart Journal* **19** Suppl K, K11-K17, 1998) and Oldgren J. et al. (*European Heart Journal* **20** 1657-66, 1999) both convey that antithrombic compounds are not always effective in treating ill patients that are afflicted with thrombin-mediated disorders. Thus, one can conclude that if a compound inhibits platelet aggregation, that observation is not sufficient to predict therapeutic efficacy in the treatment of cardiovascular disorders.
- Serneria (*Lancet* **345**, 1201-1204, 1995) discloses that aspirin is not effective to alter the incidence of myocardial ischemia in patients. This finding is relevant to the claimed invention, since aspirin is effective to both inhibit platelet aggregation, and to mitigate the severity of inflammatory responses. Thus, this reference supports the proposition that even if one can inhibit inflammatory responses, and, at the same time, inhibit platelet aggregation, one cannot "predict" success in the treatment of cardiovascular disorders.
- Mousa (*Arteriosclerosis, Thrombosis and Vascular Biology* **19**, 2535, 1999) discloses (page 2539, col 1, last sentence; also table 6) that if aspirin is administered

before initiation of arterial thrombosis, it is not effective to reduce the incidence of occlusive arterial thrombosis. This is relevant to the claimed invention, since aspirin inhibits platelet aggregation. Thus, this reference supports the proposition that even if one can inhibit platelet aggregation, one cannot "predict" success in the treatment of cardiovascular disorders.

As indicated above, applicants have also shown that the claimed compounds can stimulate (pp. 31-32) platelets to produce cGMP. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.
- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH₂ (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) **55** (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.
- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.
- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily

predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [¹²⁵I]-Nle⁴-D-Phe⁷-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

The foregoing references (Torsello, McFadyen Keith, Xiao, Lunec) show that, whether one is endeavoring to stimulate a receptor or inhibit one, the physiological consequences of such are "unpredictable".

In accordance with the foregoing, applicants limited *in vitro* data does not permit one to "predict" success in the treatment of circulatory disorders. "Undue experimentation" would be required to practice the claimed invention. It is suggested that the term "pharmaceutical" be deleted at every occurrence, and that claim 28 be cancelled.

*

Claims 19, 28, 29 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 makes reference to the term "dysfunctions of the circulatory system". This

term could potentially encompass any of the following:

atrial fibrillation, ventricular fibrillation, arteriosclerosis, atherosclerosis, angina, myocardial infarction, cardiomyopathy, endocarditis, hypertension, hypotension, myocardial ischemia, restenosis, thromboembolism, arrhythmias, and heart failure

Which are intended?

- Claim 19 recites the following:
“S-nitrosothiol derivative of penicillamine or glutathione”

This should be preceded by the indefinite article (“an”).

- Claim 29 uses the term “derivatives” in the plural, whereas the singular of this term is used in claim 19. This tends to imply that claim 29 is really drawn to a mixture of all of the compounds of claim 19. Is this intended?

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



DAVID LUKTON
PATENT EXAMINER
GROUP 1800